IFNgamma Is Critical for CAR T Cell-Mediated Myeloid Activation and Induction of Endogenous Immunity.

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Public Summary:
Chimeric antigen receptor (CAR) T cells mediate potent antigen-specific antitumor activity; however, their indirect effects on the endogenous immune system are not well characterized. Remarkably, we demonstrate that CAR T-cell treatment of mouse syngeneic glioblastoma (GBM) activates intratumoral myeloid cells and induces endogenous T-cell memory responses coupled with feed-forward propagation of CAR T-cell responses. IFNγ production by CAR T cells and IFNγ responsiveness of host immune cells are critical for tumor immune landscape remodeling to promote a more activated and less suppressive tumor microenvironment. The clinical relevance of these observations is supported by studies showing that human IL13Rα2-CAR T cells activate patient-derived endogenous T cells and monocytes/macrophages through IFNγ signaling and induce the generation of tumor-specific T-cell responses in a responding patient with GBM. These studies establish that CAR T-cell therapy has the potential to shape the tumor microenvironment, creating a context permissible for eliciting endogenous antitumor immunity. SIGNIFICANCE: Our findings highlight the critical role of IFNγ signaling for a productive CAR T-cell therapy in GBM. We establish that CAR T cells can activate resident myeloid populations and promote endogenous T-cell immunity, emphasizing the importance of host innate and adaptive immunity for CAR T-cell therapy of solid tumors.

Scientific Abstract:
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